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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


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 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  SEP 09  ACD predicted properties enhanced in REGISTRY/ZREGISTRY
 NEWS  4  OCT 03  MATHDI removed from STN
 NEWS  5  OCT 04  CA/CAplus-Canadian Intellectual Property Office (CIPO) added
                  to core patent offices
 NEWS  6  OCT 13  New CAS Information Use Policies Effective October 17, 2005
 NEWS  7  OCT 17  STN(R) AnaVist(TM), Version 1.01, allows the export/download
                  of CAplus documents for use in third-party analysis and
                  visualization tools
 NEWS  8  OCT 27  Free KWIC format extended in full-text databases
 NEWS  9  OCT 27  DIOGENES content streamlined
 NEWS 10  OCT 27  EPFULL enhanced with additional content
 NEWS 11  NOV 14  CA/CAplus - Expanded coverage of German academic research
 NEWS 12  NOV 30  REGISTRY/ZREGISTRY on STN(R) enhanced with experimental
                  spectral property data
 NEWS 13  DEC 05  CASREACT(R) - Over 10 million reactions available

 NEWS EXPRESS  DECEMBER 02 CURRENT VERSION FOR WINDOWS IS V8.01,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 02 DECEMBER 2005.
               V8.0 USERS CAN OBTAIN THE UPGRADE TO V8.01 AT
               http://download.cas.org/express/v8.0-Discover/

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FILE 'HOME' ENTERED AT 09:22:46 ON 14 DEC 2005

=> file reg
COST IN U.S. DOLLARS                                  SINCE FILE     TOTAL
                                                           ENTRY   SESSION
FULL ESTIMATED COST                                         0.21      0.21
```

```
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```
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STRUCTURE FILE UPDATES:    13 DEC 2005  HIGHEST RN 869843-02-7
DICTIONARY FILE UPDATES:  13 DEC 2005  HIGHEST RN 869843-02-7

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*******************************************************************
*                                                                 *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                 *
*******************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> E "SULINDAC"/CN 25
E1             1      SULIKOL K/CN
E2             1      SULIN/CN
E3             1 --> SULINDAC/CN
E4             1      SULINDAC B Ω-N-METHYL-L-ARGININE SALT/CN
E5             1      SULINDAC B Ω-N-NITRO-L-ARGININE METHYL ESTER SALT/CN
E6             1      SULINDAC B Ω-N-NITRO-L-ARGININE SALT/CN
E7             1      SULINDAC ETHYL ESTER/CN
E8             1      SULINDAC SODIUM/CN
E9             1      SULINDAC SULFIDE/CN
E10            1      SULINDAC SULFONE/CN
E11            1      SULINDAC SULFOXIDE/CN
E12            1      SULINDAC-QUINOLINE/CN
E13            1      SULINEX/CN
E14            1      SULINOL/CN
E15            1      SULIODOVIZOL/CN
E16            1      SULISATIN/CN
E17            1      SULISATIN DISODIUM SALT/CN
E18            1      SULISATIN SODIUM/CN
E19            1      SULISATINE SODIUM/CN
E20            1      SULISOBENZONE/CN
E21            1      SULJEX/CN
E22            1      SULKA/CN
E23            1      SULKA K BOLUSES/CN
E24            1      SULKA N/CN
```

```
E25          1     SULKOR/CN

=> S E3
L1           1 SULINDAC/CN

=> file caplus
COST IN U.S. DOLLARS                                  SINCE FILE     TOTAL
                                                           ENTRY   SESSION
FULL ESTIMATED COST                                         5.03      5.24

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FILE COVERS 1907 - 14 Dec 2005  VOL 143 ISS 25
FILE LAST UPDATED: 13 Dec 2005  (20051213/ED)

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=> s l1
L2        1426 L1

=> s gastrointestingal or esophag? or gastic? or intestin? or colorect?
             2 GASTROINTESTINGAL
         15568 ESOPHAG?
             4 GASTIC?
        239459 INTESTIN?
         18675 COLORECT?
L3      254068 GASTROINTESTINGAL OR ESOPHAG? OR GASTIC? OR INTESTIN? OR COLOREC
               T?

=> s cancer? or tumor? or neoplas? or polyp?
        277857 CANCER?
        411659 TUMOR?
        431921 NEOPLAS?
        438716 POLYP?
L4     1099978 CANCER? OR TUMOR? OR NEOPLAS? OR POLYP?

=> s l4 and l3
L5       65506 L4 AND L3

=> s l5 and l2
L6         234 L5 AND L2

=> s oral?
L7      243958 ORAL?

=> s l7 and l6
```

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L8          30 L7 AND L6

=> s l2 (l) l4
L9         186 L2 (L) L4

=> s l9 and l3
L10        121 L9 AND L3

=> s l10 and l7
L11         14 L10 AND L7

=> s l14 not py>2002
L14 NOT FOUND
The L-number entered could not be found.  To see the definition
of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s l11 not py>2002
       3346380 PY>2002
L12          9 L11 NOT PY>2002

=> d ibib 1-4

L12  ANSWER 1 OF 9  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2002:723268  CAPLUS
DOCUMENT NUMBER:          138:13001
TITLE:                    A mouse model of human oral-
                          esophageal cancer
AUTHOR(S):                Opitz, Oliver G.; Harada, Hideki; Suliman, Yasir;
                          Rhoades, Ben; Sharpless, Norman E.; Kent, Ralph;
                          Kopelovich, Levy; Nakagawa, Hiroshi; Rustgi, Anil K.
CORPORATE SOURCE:         Division of Gastroenterology, University of
                          Pennsylvania, Philadelphia, PA, 19104-2144, USA
SOURCE:                   Journal of Clinical Investigation (2002), 110(6),
                          761-769
                          CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER:                American Society for Clinical Investigation
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          44    THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12  ANSWER 2 OF 9  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2002:259707  CAPLUS
DOCUMENT NUMBER:          136:379639
TITLE:                    Primary chemoprevention of familial adenomatous
                          polyposis with sulindac
AUTHOR(S):                Giardiello, Francis M.; Yang, Vincent W.; Hylind,
                          Linda M.; Krush, Anne J.; Petersen, Gloria M.;
                          Trimbath, Jill D.; Piantadosi, Steven; Garrett,
                          Elizabeth; Geiman, Deborah E.; Hubbard, Walter;
                          Offerhaus, Johan A.; Hamilton, Stanley R.
CORPORATE SOURCE:         Dep. Med., Johns Hopkins Univ. Sch. Med., Baltimore,
                          MD, USA
SOURCE:                   New England Journal of Medicine (2002), 346(14),
                          1054-1059
                          CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER:                Massachusetts Medical Society
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          23    THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12  ANSWER 3 OF 9  CAPLUS  COPYRIGHT 2005 ACS on STN
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```
ACCESSION NUMBER:         2001:564792  CAPLUS
DOCUMENT NUMBER:          135:127230
TITLE:                    Method for inhibiting a tumor
INVENTOR(S):              Nair, Muraleedharan G.; Bourquin, Leslie D.; Seeram,
                          Navindra P.; Kang, Soo-Young
PATENT ASSIGNEE(S):       Michigan State University, USA
SOURCE:                   PCT Int. Appl., 27 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

    PATENT NO.            KIND   DATE       APPLICATION NO.        DATE
    ---------------       ----   --------   --------------------   --------
    WO 2001054516          A1    20010802   WO 2001-US1196         20010112
        W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
            CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
            HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
            LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
            SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
            ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
            DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
            BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
    CA 2398389             AA    20010802   CA 2001-2398389        20010112
PRIORITY APPLN. INFO.:                      US 2000-494077      A  20000128
                                            WO 2001-US1196      W  20010112
REFERENCE COUNT:          2      THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS
                                 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12  ANSWER 4 OF 9  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2001:476884  CAPLUS
DOCUMENT NUMBER:          135:282815
TITLE:                    Sulindac in familial adenomatous polyposis: Evaluation
                          by nuclear morphometry
AUTHOR(S):                Fernandez-Lopez, F.; Conde-Freire, R.; Cadarso-Suarez,
                          C.; Garcia-Iglesias, J.; Puente-Dominguez, J. L.;
                          Potel-Lesquereux, J.
CORPORATE SOURCE:         General Surgery Department, Hospital Clinico
                          Universitario, Santiago de Compostela, Spain
SOURCE:                   European Journal of Surgery (2001), 167(5), 375-381
                          CODEN: EUJSEH; ISSN: 1102-4151
PUBLISHER:                Taylor & Francis Ltd.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          31     THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS
                                 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> d ibib 5-9

L12  ANSWER 5 OF 9  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2000:260877  CAPLUS
DOCUMENT NUMBER:          133:217169
TITLE:                    Sulindac and acetylsalicylic acid (ASA) - clinical
                          relevance in familial adenomatous polyposis
AUTHOR(S):                Winde, G.
CORPORATE SOURCE:         Klinik und Poliklinik fur Allgemeine Chirurgie der
                          WWU, Munster, D-48129, Germany
SOURCE:                   Falk Symposium (1999), 109(Colorectal Cancer), 235-255
                          CODEN: FASYDI; ISSN: 0161-5580
PUBLISHER:                Kluwer Academic Publishers
```

DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 91 THERE ARE 91 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:147314 CAPLUS
DOCUMENT NUMBER: 132:273995
TITLE: Inhibition of rat colon tumors by sulindac and sulindac sulfone is independent of K-ras (codon 12) mutation
AUTHOR(S): De Jong, Tanya A.; Skinner, Stewart A.; Malcontenti-Wilson, Cathy; Vogiagis, Daphne; Bailey, Michael; Van Driel, Ian R.; O'Brien, Paul E.
CORPORATE SOURCE: Department of Surgery, Monash University Medical School, Melbourne, 3181, Australia
SOURCE: American Journal of Physiology (2000), 278(2, Pt. 1), G266-G272
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:18902 CAPLUS
DOCUMENT NUMBER: 132:44655
TITLE: Rectal epithelial apoptosis in familial adenomatous polyposis patients treated with sulindac
AUTHOR(S): Keller, J. J.; Offerhaus, G. J. A.; Polak, M.; Goodman, S. N.; Zahurak, M. L.; Hylind, L. M.; Hamilton, S. R.; Giardiello, F. M.
CORPORATE SOURCE: Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Gut (1999), 45(6), 822-828
CODEN: GUTTAK; ISSN: 0017-5749
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:277228 CAPLUS
DOCUMENT NUMBER: 124:331957
TITLE: Sulindac induced regression of **colorectal** adenomas in familial adenomatous polyposis: Evaluation of predictive factors
AUTHOR(S): Giardiello, F. M.; Offerhaus, J. A.; Tersmette, A. C.; Hylind, L. M.; Krush, A. J.; Brensinger, J. D.; Booker, S. V.; Hamilton, S. R.
CORPORATE SOURCE: School Medicine, Johns Hopkins University, Baltimore, MD, 21287, USA
SOURCE: Gut (1996), 38(4), 578-581
CODEN: GUTTAK; ISSN: 0017-5749
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

L12 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:529697 CAPLUS
DOCUMENT NUMBER: 115:129697

```
TITLE:                   Lung tumorigenicity of NNK given orally to
                         A/J mice: its application to chemopreventive efficacy
                         studies
AUTHOR(S):               Castonguay, Andre; Pepin, Pierrot; Stoner, Gary D.
CORPORATE SOURCE:        Sch. Pharm., Laval Univ., Quebec, QC, G1K 7P4, Can.
SOURCE:                  Experimental Lung Research (1991), 17(2), 485-99
                         CODEN: EXLRDA; ISSN: 0190-2148
DOCUMENT TYPE:           Journal
LANGUAGE:                English

=> d abs 9

L12  ANSWER 9 OF 9  CAPLUS  COPYRIGHT 2005 ACS on STN
AB   The ability of five chemopreventive agents to inhibit 4-
     (methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung tumors in
     A/J mice was determined  The carcinogen was administered in the drinking water
     during 7 wk (at doses of 9.2 to 3.1 mg/mouse).  Three chemopreventive
     agents: (dose, g/kg diet) ellagic acid (4.0), 2(3)-BHA (5.0), and sulindac
     (0.13) inhibited the multiplicity of lung adenomas by 52, 88, and 52%,
     resp., when compared to NNK controls.  β-Carotene + retinol (2.14 +
     0.009), in combination, and selenium (0.0022) were ineffective.  NNK was
     absorbed more rapidly from the duodenum than from the stomach and was
     metabolized in both tissues.  The activation of NNK by α-carbon
     hydroxylation and its deactivation by pyridine N-oxidation was more extensive
     in the duodenum than in the stomach.  Carbonyl reduction of NNK was 10 times
     higher in the duodenum.  Liver microsomes were more active than lung
     microsomes in the α-carbon hydroxylation of NNK, suggesting that
     some liver isoenzymes of cytochrome P 450 have a high affinity for NNK.
     Pyridine N-oxidation was five times more extensive in lung microsomes than in
     liver microsomes.  Collectively, these results demonstrate that NNK given
     orally to A/J mice provides a suitable model from which to assess
     the relative activity and mechanisms of action of chemopreventive agents
     in pulmonary carcinogenesis.

=> d kwic 9

L12  ANSWER 9 OF 9  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Lung tumorigenicity of NNK given orally to A/J mice:  its
     application to chemopreventive efficacy studies
AB   . . .  N-oxidation was five times more extensive in lung microsomes than in
     liver microsomes.  Collectively, these results demonstrate that NNK given
     orally to A/J mice provides a suitable model from which to assess
     the relative activity and mechanisms of action of chemopreventive.  . .
IT   Intestine, metabolism
        (duodenum, (methylnitrosamino)(pyridyl)butanone metabolism by,
        chemopreventive agents agents against lung neoplasm effect on)
IT   68-26-8, Retinol   476-66-4, Ellagic acid   7235-40-7, β-Carotene
     14124-67-5, Selenite   25013-16-5 38194-50-2, Sulindac
     RL: BIOL (Biological study)
        ((methylnitrosamino)(pyridyl)butanone-induced lung neoplasm
        response to)

=> d ibib abs keic 8
'KEIC' IS NOT A VALID FORMAT FOR FILE 'CAPLUS'

The following are valid formats:

ABS --------- GI and AB
ALL --------- BIB, AB, IND, RE
APPS -------- AI, PRAI
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BIB --------- AN, plus Bibliographic Data and PI table (default)
CAN --------- List of CA abstract numbers without answer numbers
CBIB -------- AN, plus Compressed Bibliographic Data
DALL -------- ALL, delimited (end of each field identified)
DMAX -------- MAX, delimited for post-processing
FAM --------- AN, PI and PRAI in table, plus Patent Family data
FBIB -------- AN, BIB, plus Patent FAM
IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers;
              SCAN must be entered on the same line as the DISPLAY,
              e.g., D SCAN or DISPLAY SCAN)
STD --------- BIB, IPC, and NCL

IABS -------- ABS, indented with text labels
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
ISTD -------- STD, indented with text labels

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

HIT --------- Fields containing hit terms
HITIND ------ IC, ICA, ICI, NCL, CC and index field (ST and IT)
              containing hit terms
HITRN ------- HIT RN and its text modification
HITSTR ------ HIT RN, its text modification, its CA index name, and
              its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
              its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
KWIC -------- Hit term plus 20 words on either side
OCC --------- Number of occurrence of hit term and field in which it occurs

To display a particular field or fields, enter the display field
codes.  For a list of the display field codes, enter HELP DFIELDS at
an arrow prompt (=>).  Examples of formats include: TI; TI,AU; BIB,ST;
TI,IND; TI,SO.  You may specify the format fields in any order and the
information will be displayed in the same order as the format
specification.

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FHITSTR, HITSEQ, FHITSEQ, KWIC, and OCC) may be used with DISPLAY ACC
to view a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):end

=> d ibib abs kwic 8

L12  ANSWER 8 OF 9  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         1996:277228  CAPLUS
DOCUMENT NUMBER:          124:331957
TITLE:                    Sulindac induced regression of colorectal
                          adenomas in familial adenomatous polyposis: Evaluation
```

of predictive factors

AUTHOR(S): Giardiello, F. M.; Offerhaus, J. A.; Tersmette, A. C.; Hylind, L. M.; Krush, A. J.; Brensinger, J. D.; Booker, S. V.; Hamilton, S. R.

CORPORATE SOURCE: School Medicine, Johns Hopkins University, Baltimore, MD, 21287, USA

SOURCE: Gut (1996), 38(4), 578-581
CODEN: GUTTAK; ISSN: 0017-5749

PUBLISHER: BMJ Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background-Sulindac, a non-steroidal anti-inflammatory drug, causes regression of **colorectal** adenomas in patients with familial adenomatous polyposis (FAP) but the response is variable. Specific clin. factors predictive of sulindac induced regression have not been studied. Methods-22 patients with FAP were given sulindac 150 mg **orally** twice a day. Polyp number and size were determined before treatment and at three months. The relation of nine clin. factors to polyp regression (per cent of baseline polyp number after treatment) was evaluated by univariate and multivariate anal. Results-After three months of sulindac, polyp number had decreased to 45 per cent of baseline and polyp size to 50 per cent of baseline (p<0.001 and p<0.01, resp.). Univariate anal. showed greater polyp regression in older patients (p=0.004), those with previous colectomy and ileorectal anastomosis (p=0.001), and patients without identifiable mutation of the APC gene responsible for FAP (p=0.05). With multivariate regression anal., response to sulindac treatment was associated with previous subtotal colectomy. Conclusions-Sulindac treatment seems effective in producing regression of **colorectal** adenomas of FAP patients with previous subtotal colectomy regardless of baseline polyp number and size. Changed sulindac metabolism, reduced area of the target mucosa, or changed epithelial characteristics after ileorectal anastomosis may explain these findings.

TI Sulindac induced regression of **colorectal** adenomas in familial adenomatous polyposis: Evaluation of predictive factors

AB Background-Sulindac, a non-steroidal anti-inflammatory drug, causes regression of **colorectal** adenomas in patients with familial adenomatous polyposis (FAP) but the response is variable. Specific clin. factors predictive of sulindac induced regression have not been studied. Methods-22 patients with FAP were given sulindac 150 mg **orally** twice a day. Polyp number and size were determined before treatment and at three months. The relation of nine clin. factors to polyp regression (per cent of baseline polyp number after treatment) was evaluated by univariate and multivariate anal. Results-After three months of sulindac, polyp number had decreased to 45 per cent of baseline and polyp size to 50 per cent of baseline (p<0.001 and p<0.01, resp.). Univariate anal. showed greater polyp regression in older patients (p=0.004), those with previous colectomy and ileorectal anastomosis (p=0.001), and patients without identifiable mutation of the APC gene responsible for FAP (p=0.05). With multivariate regression anal., response to sulindac treatment was associated with previous subtotal colectomy. Conclusions-Sulindac treatment seems effective in producing regression of **colorectal** adenomas of FAP patients with previous subtotal colectomy regardless of baseline polyp number and size. Changed sulindac metabolism, reduced area of the target mucosa, or changed epithelial characteristics after ileorectal anastomosis may explain these findings.

ST sulindac **colorectal** adenomas adenomatous polyposis

IT Neoplasm inhibitors
(large **intestine**, sulindac induced regression of **colorectal** adenomas in familial adenomatous polyposis in humans)

IT **Intestine**, neoplasm

(large, inhibitors, sulindac induced regression of **colorectal** adenomas in familial adenomatous polyposis in humans)

IT **38194-50-2**, Sulindac
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sulindac induced regression of **colorectal** adenomas in familial adenomatous **polyposis** in humans)

=> d ibib abs kwic 2

L12 ANSWER 2 OF 9 CAPLUS
ACCESSION NUMBER: 2002:259707 CAPLUS
DOCUMENT NUMBER: 136:379639
TITLE: Primary chemoprevention of familial adenomatous polyposis with sulindac
AUTHOR(S): Giardiello, Francis M.; Yang, Vincent W.; Hylind, Linda M.; Krush, Anne J.; Petersen, Gloria M.; Trimbath, Jill D.; Piantadosi, Steven; Garrett, Elizabeth; Geiman, Deborah E.; Hubbard, Walter; Offerhaus, Johan A.; Hamilton, Stanley R.
CORPORATE SOURCE: Dep. Med., Johns Hopkins Univ. Sch. Med., Baltimore, MD, USA
SOURCE: New England Journal of Medicine (2002), 346(14), 1054-1059
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Familial adenomatous polyposis is caused by a germ-line mutation in the adenomatous polyposis coli gene and is characterized by the development of hundreds of **colorectal** adenomas and, eventually, **colorectal** cancer. Nonsteroidal antiinflammatory drugs can cause regression of adenomas, but whether they can prevent adenomas is unknown. Methods: The authors conducted a randomized, double-blind, placebo-controlled study of 41 young subjects (age range, 8 to 25 yr) who were genotypically affected with familial adenomatous polyposis but phenotypically unaffected. The subjects received either 75 or 150 mg of sulindac **orally** twice a day or identical-appearing placebo tablets for 48 mo. The number and size of new adenomas and side effects of therapy were evaluated every four months for four years, and the levels of five major prostaglandins were serially measured in biopsy specimens of normal-appearing **colorectal** mucosa. Results: After four years of treatment, the average rate of compliance exceeded 76 % in the sulindac group, and mucosal prostaglandin levels were lower in this group than in the placebo group. During the course of the study, adenomas developed in 9 of 21 subjects (43 %) in the sulindac group and 11 of 20 subjects in the placebo group (55 %) (P = 0.54). There were no significant differences in the mean number (P = 0.69) or size (P = 0.17) of polyps between the groups. Sulindac did not slow the development of adenomas, according to an evaluation involving linear longitudinal methods. Conclusions: Standard doses of sulindac did not prevent the development of adenomas in subjects with familial adenomatous polyposis.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Background: Familial adenomatous polyposis is caused by a germ-line mutation in the adenomatous polyposis coli gene and is characterized by the development of hundreds of **colorectal** adenomas and, eventually, **colorectal** cancer. Nonsteroidal antiinflammatory drugs can cause regression of adenomas, but whether they can prevent adenomas is unknown. Methods: The authors conducted a randomized, double-blind, placebo-controlled study of 41 young subjects (age range, 8

to 25 yr) who were genotypically affected with familial adenomatous polyposis but phenotypically unaffected. The subjects received either 75 or 150 mg of sulindac **orally** twice a day or identical-appearing placebo tablets for 48 mo. The number and size of new adenomas and side effects of therapy were evaluated every four months for four years, and the levels of five major prostaglandins were serially measured in biopsy specimens of normal-appearing **colorectal** mucosa. Results: After four years of treatment, the average rate of compliance exceeded 76 % in the sulindac group, and mucosal prostaglandin levels were lower in this group than in the placebo group. During the course of the study, adenomas developed in 9 of 21 subjects (43 %) in the sulindac group and 11 of 20 subjects in the placebo group (55 %) (P = 0.54). There were no significant differences in the mean number (P = 0.69) or size (P = 0.17) of polyps between the groups. Sulindac did not slow the development of adenomas, according to an evaluation involving linear longitudinal methods. Conclusions: Standard doses of sulindac did not prevent the development of adenomas in subjects with familial adenomatous polyposis.

```
IT   Prostaglandins
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (colorectal mucosa prostaglandin levels as measure of
        sulindac local effect in humans with familial adenomatous polyposis)
IT   Antitumor agents
        (colorectal, adenoma; primary chemoprevention of familial
        adenomatous polyposis with sulindac in humans)
IT   Intestine, neoplasm
        (colorectal, inhibitors, adenoma; primary chemoprevention of
        familial adenomatous polyposis with sulindac in humans)
IT   Intestine, neoplasm
        (familial polyposis; primary chemoprevention of familial adenomatous
        polyposis with sulindac in humans)
IT   Intestine
        (large, mucosa; colorectal mucosa prostaglandin levels as
        measure of sulindac local effect in humans with familial adenomatous
        polyposis)
IT   363-24-6, Prostaglandin E2   551-11-1, Prostaglandin F2α
     13367-85-6, Prostaglandin B2   41598-07-6, Prostaglandin D2   58962-34-8,
     6-keto-Prostaglandin F1α
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (colorectal mucosa prostaglandin levels as measure of
        sulindac local effect in humans with familial adenomatous polyposis)
IT   38194-50-2, Sulindac
     RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological
     activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (primary chemoprevention of familial adenomatous polyposis
        with sulindac in humans)


=> d his

     (FILE 'HOME' ENTERED AT 09:22:46 ON 14 DEC 2005)

     FILE 'REGISTRY' ENTERED AT 09:22:55 ON 14 DEC 2005
                E "SULINDAC"/CN 25
L1              1 S E3

     FILE 'CAPLUS' ENTERED AT 09:23:34 ON 14 DEC 2005
L2           1426 S L1
L3         254068 S GASTROINTESTINGAL OR ESOPHAG? OR GASTIC? OR INTESTIN? OR COLO
L4        1099978 S CANCER? OR TUMOR? OR NEOPLAS? OR POLYP?
L5          65506 S L4 AND L3
L6            234 S L5 AND L2
L7         243958 S ORAL?
L8             30 S L7 AND L6
```

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L9          186 S L2 (L) L4
L10         121 S L9 AND L3
L11          14 S L10 AND L7
L12           9 S L11 NOT PY>2002

=> s lipsom? or microspher? or encapsulat? or polymer?
           74 LIPSOM?
        27180 MICROSPHER?
        55572 ENCAPSULAT?
      1820552 POLYMER?
        84067 POLYMD
        84067 POLYMD
                (POLYMD)
        31147 POLYMG
       326031 POLYMN
         8505 POLYMNS
       327118 POLYMN
                (POLYMN OR POLYMNS)
      1885881 POLYMER?
                (POLYMER? OR POLYMD OR POLYMG OR POLYMN)
L13   1945587 LIPSOM? OR MICROSPHER? OR ENCAPSULAT? OR POLYMER?

=> s l13 and l12
L14           0 L13 AND L12

=> s l4 and l2
L15         443 L4 AND L2

=> s l9 and l13
L16          12 L9 AND L13

=> s l16 not py>2002
      3346380 PY>2002
L17           3 L16 NOT PY>2002

=> d ibib 1-3

L17  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2001:430708  CAPLUS
DOCUMENT NUMBER:          135:236055
TITLE:                    Rat colorectal tumors treated with a range of
                          nonsteroidal anti-inflammatory drugs show altered
                          cyclooxygenase-2 and cyclooxygenase-1 splice variant
                          mRNA expression levels
AUTHOR(S):                Vogiagis, Daphne; Brown, Wendy; Glare, Eric M.;
                          O'Brien, Paul E.
CORPORATE SOURCE:         Department of Surgery, Monash University Medical
                          School, Alfred Hospital, Prahran, 3181, Australia
SOURCE:                   Carcinogenesis (2001), 22(6), 869-874
                          CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER:                Oxford University Press
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          49     THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS
                                 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17  ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         1998:457250  CAPLUS
DOCUMENT NUMBER:          129:76490
TITLE:                    Method for treating a tumor with a chemotherapeutic
                          agent and nonemulsified ultrapurified
                          polymerized hemoglobin solution
INVENTOR(S):              Teicher, Beverly A.; Rausch, Carl W.; Hopkins, Robert
```

E., II
PATENT ASSIGNEE(S): Dana-Farber Cancer Institute, USA; Biopure Corp.
SOURCE: U.S., 16 pp., Cont.-in-part of U. S. Ser. No. 94,501.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 5776898	A	19980707	US 1995-477110		19950607
US 5679638	A	19971021	US 1993-94501		19930720
PRIORITY APPLN. INFO.:			US 1991-699769	A2	19910514
			US 1993-94501	A2	19930720

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:689536 CAPLUS
DOCUMENT NUMBER: 127:326520
TITLE: Method for treating a tumor with a chemotherapeutic agent
INVENTOR(S): Teicher, Beverly A.; Rausch, Carl W.; Hopkins, Robert E., II
PATENT ASSIGNEE(S): Biopure Corporation, USA; Dana Farber Cancer Institute
SOURCE: U.S., 12 pp., Cont.-in-part of U.S. Ser. No. 699,769,abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 5679638	A	19971021	US 1993-94501		19930720
US 5776898	A	19980707	US 1995-477110		19950607
PRIORITY APPLN. INFO.:			US 1991-699769	B2	19910514
			US 1993-94501	A2	19930720

=> d ibib abs kwic 1

L17 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:430708 CAPLUS
DOCUMENT NUMBER: 135:236055
TITLE: Rat colorectal tumors treated with a range of nonsteroidal anti-inflammatory drugs show altered cyclooxygenase-2 and cyclooxygenase-1 splice variant mRNA expression levels
AUTHOR(S): Vogiagis, Daphne; Brown, Wendy; Glare, Eric M.; O'Brien, Paul E.
CORPORATE SOURCE: Department of Surgery, Monash University Medical School, Alfred Hospital, Prahran, 3181, Australia
SOURCE: Carcinogenesis (2001), 22(6), 869-874
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce tumor mass by increasing tumor cell apoptosis and decreasing cell proliferation. The classically recognized targets for NSAID action are the two isoforms of

the cyclooxygenase (COX) gene, which is responsible for prostaglandin production In the rat, the COX-1 gene expresses an alternatively spliced mRNA COX-1 splice variant (SV) which may, at best, code for a truncated COX-1 protein. Previously, it was reported that COX-1SV mRNA is differentially expressed in the ageing stomach. In this study, carcinogen-treated rats were treated for 23 wk with the NSAIDs celecoxib, sulindac or sulindac sulfone, while untreated rats received vehicle alone. The nos. and vols. of tumor per animal were recorded and histol. was performed. The competitive **polymerase** chain reaction, was used to determine whether COX gene expression was altered in colorectal tumors and in regions of adjacent and distant macroscopically normal intestine, from vehicle- or NSAID-treated rats. In addition, COX-1 and COX-2 were immunolocalized in the same tumor and normal colonic tissue. Tumors from animals treated with vehicle or celecoxib expressed elevated levels of COX-2 mRNA in comparison with the adjacent normal mucosa. In contrast, tumors from sulindac- and sulindac sulfone-treated rats expressed less COX-2 mRNA than tumors from vehicle-treated rats. The expression of COX-1 mRNA remained unchanged in all tissues examined However, COX-1SV mRNA contents were elevated in colorectal tumors and reduced after NSAID treatment to the values in normal colonic mucosa. The results indicate that the antineoplastic actions of NSAIDs may be attributed to COX-dependent and/or COX-independent mechanisms of action. The presence and differential expression of COX-1SV mRNA was also demonstrated in colon tumors. COX-1SV mRNA represents 2% of the total COX-1 mRNA expressed and its role in colon cancer remains to be established.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce tumor mass by increasing tumor cell apoptosis and decreasing cell proliferation. The classically recognized targets for NSAID action are the two isoforms of the cyclooxygenase (COX) gene, which is responsible for prostaglandin production In the rat, the COX-1 gene expresses an alternatively spliced mRNA COX-1 splice variant (SV) which may, at best, code for a truncated COX-1 protein. Previously, it was reported that COX-1SV mRNA is differentially expressed in the ageing stomach. In this study, carcinogen-treated rats were treated for 23 wk with the NSAIDs celecoxib, sulindac or sulindac sulfone, while untreated rats received vehicle alone. The nos. and vols. of tumor per animal were recorded and histol. was performed. The competitive **polymerase** chain reaction, was used to determine whether COX gene expression was altered in colorectal tumors and in regions of adjacent and distant macroscopically normal intestine, from vehicle- or NSAID-treated rats. In addition, COX-1 and COX-2 were immunolocalized in the same tumor and normal colonic tissue. Tumors from animals treated with vehicle or celecoxib expressed elevated levels of COX-2 mRNA in comparison with the adjacent normal mucosa. In contrast, tumors from sulindac- and sulindac sulfone-treated rats expressed less COX-2 mRNA than tumors from vehicle-treated rats. The expression of COX-1 mRNA remained unchanged in all tissues examined However, COX-1SV mRNA contents were elevated in colorectal tumors and reduced after NSAID treatment to the values in normal colonic mucosa. The results indicate that the antineoplastic actions of NSAIDs may be attributed to COX-dependent and/or COX-independent mechanisms of action. The presence and differential expression of COX-1SV mRNA was also demonstrated in colon tumors. COX-1SV mRNA represents 2% of the total COX-1 mRNA expressed and its role in colon cancer remains to be established.

IT **38194-50-2**, Sulindac 59973-80-7, Sulindac sulfone 169590-42-5, Celecoxib
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(colorectal **tumors** treated with nonsteroidal anti-inflammatory drugs show altered cyclooxygenase-2 and cyclooxygenase-1 splice variant mRNA expression)

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=> file medline
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    64.77      70.01

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)        SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -3.65      -3.65

FILE 'MEDLINE' ENTERED AT 09:35:28 ON 14 DEC 2005

 FILE LAST UPDATED: 8 DEC 2005 (20051208/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 will soon be available.  For details
 on the 2005 reload, enter HELP RLOAD at an arrow promt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s SULINDAC/CN
L18          919 SULINDAC/CN

=> s cancer? or tumor? or neoplas? or polyp?
        547932 CANCER?
        758323 TUMOR?
       1455946 NEOPLAS?
        155044 POLYP?
L19    1879233 CANCER? OR TUMOR? OR NEOPLAS? OR POLYP?

=> s gastrointestingal or esophag? or gastic? or intestin? or colorect?
             1 GASTROINTESTINGAL
        101857 ESOPHAG?
            50 GASTIC?
        293936 INTESTIN?
         45036 COLORECT?
L20     428581 GASTROINTESTINGAL OR ESOPHAG? OR GASTIC? OR INTESTIN? OR COLOREC
               T?

=> s l19 and l20
L21     125328 L19 AND L20

=> s l21 and l18
L22          175 L21 AND L18

=> s liposom? or microspher? or encapsulat? or polymer?
         30623 LIPOSOM?
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         15072 ENCAPSULAT?
        351141 POLYMER?
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L23     407843 LIPOSOM? OR MICROSPHER? OR ENCAPSULAT? OR POLYMER?

=> s l23 and l22
L24            8 L23 AND L22

=> s l24 not py>2002
       1733376 PY>2002
L25            6 L24 NOT PY>2002

=> d ibib 1-3

L25  ANSWER 1 OF 6     MEDLINE on STN
ACCESSION NUMBER:    2002696841     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 12458338
TITLE:               Effects of long-term administration of sulindac on APC mRNA
                     and apoptosis in colons of rats treated with azoxymethane.
AUTHOR:              Kishimoto Y; Yashima K; Morisawa T; Ohishi T; Marumoto A;
                     Sano A; Idobe-Fujii Y; Miura N; Shiota G; Murawaki Y;
                     Hasegawa J
CORPORATE SOURCE:    Division of Pharmacotherapeutics, Department of
                     Pathophysiological and Therapeutic Science, Faculty of
                     Medicine, Tottori University, 86 Nishicho, Yonago 683-8503,
                     Japan.. ykishimo@grape.med.tottori-u.ac.jp
SOURCE:              Journal of cancer research and clinical oncology, (2002
                     Nov) 128 (11) 589-95.  Electronic Publication: 2002-10-04.
                     Journal code: 7902060. ISSN: 0171-5216.
PUB. COUNTRY:        Germany: Germany, Federal Republic of
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200301
ENTRY DATE:          Entered STN: 20021217
                     Last Updated on STN: 20030118
                     Entered Medline: 20030117

L25  ANSWER 2 OF 6     MEDLINE on STN
ACCESSION NUMBER:    2001065648     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 11093808
TITLE:               Growth-suppressive effect of non-steroidal
                     anti-inflammatory drugs on 11 colon-cancer cell
                     lines and fluorescence differential display of genes whose
                     expression is influenced by sulindac.
AUTHOR:              Akashi H; Han H J; Iizaka M; Nakamura Y
CORPORATE SOURCE:    Laboratory of Molecular Medicine, Human Genome Center,
                     Institute of Medical Science, University of Tokyo, Tokyo,
                     Japan.
SOURCE:              International journal of cancer. Journal international du
                     cancer, (2000 Dec 15) 88 (6) 873-80.
                     Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200012
ENTRY DATE:          Entered STN: 20010322
                     Last Updated on STN: 20010322
                     Entered Medline: 20001222

L25  ANSWER 3 OF 6     MEDLINE on STN
ACCESSION NUMBER:    2001064500     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 11076880
TITLE:               Sulindac and a cyclooxygenase-2 inhibitor, etodolac,
                     increase APC mRNA in the colon of rats treated with
```

azoxymethane.
AUTHOR: Kishimoto Y; Takata N; Jinnai T; Morisawa T; Shiota G; Kawasaki H; Hasegawa J
CORPORATE SOURCE: Department of Clinical Pharmacology, Faculty of Medicine, Tottori University, 86 Nishicho, Yonago 683-8503, Japan.. ykishimo@grape.med.tottori-u.ac.jp
SOURCE: Gut, (2000 Dec) 47 (6) 812-9.
Journal code: 2985108R. ISSN: 0017-5749.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001222

=> d ibib 4-6

L25 ANSWER 4 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2000295032 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10833474
TITLE: Par-4, a proapoptotic gene, is regulated by NSAIDs in human colon carcinoma cells.
AUTHOR: Zhang Z; DuBois R N
CORPORATE SOURCE: Division of Gastroenterology, Department of Medicine and Cell Biology, Vanderbilt University Medical Center, Veterans Affairs Medical Center, Nashville, Tennessee, USA.
CONTRACT NUMBER: DK47297 (NIDDK)
P30 CA68485 (NCI)
PO CA77839 (NCI)
SOURCE: Gastroenterology, (2000 Jun) 118 (6) 1012-7.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20021219
Entered Medline: 20000621

L25 ANSWER 5 OF 6 MEDLINE on STN
ACCESSION NUMBER: 1999333404 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10403841
TITLE: Redistribution of activated caspase-3 to the nucleus during butyric acid-induced apoptosis.
AUTHOR: Mandal M; Adam L; Kumar R
CORPORATE SOURCE: Cell Growth Regulation Laboratory, University of Texas M.D. Anderson Cancer Center, Houston, Texas, 77030, USA.
SOURCE: Biochemical and biophysical research communications, (1999 Jul 14) 260 (3) 775-80.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990827
Last Updated on STN: 20020420
Entered Medline: 19990816

L25 ANSWER 6 OF 6 MEDLINE on STN
ACCESSION NUMBER: 96334961 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8707116
TITLE: Sulindac increases the expression of APC mRNA in malignant colonic epithelial cells: an in vitro study.
AUTHOR: Schnitzler M; Dwight T; Robinson B G
CORPORATE SOURCE: Molecular Genetics Unit, Kolling Institute of Medical Research, Royal North Shore Hospital, St Leonards, NSW, Australia.
SOURCE: Gut, (1996 May) 38 (5) 707-13.
Journal code: 2985108R. ISSN: 0017-5749.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960919
Last Updated on STN: 19970203
Entered Medline: 19960910

=> d ibib abs kwic 4

L25 ANSWER 4 OF 6 MEDLINE on STN
ACCESSION NUMBER: 2000295032 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10833474
TITLE: Par-4, a proapoptotic gene, is regulated by NSAIDs in human colon carcinoma cells.
AUTHOR: Zhang Z; DuBois R N
CORPORATE SOURCE: Division of Gastroenterology, Department of Medicine and Cell Biology, Vanderbilt University Medical Center, Veterans Affairs Medical Center, Nashville, Tennessee, USA.
CONTRACT NUMBER: DK47297 (NIDDK)
P30 CA68485 (NCI)
PO CA77839 (NCI)
SOURCE: Gastroenterology, (2000 Jun) 118 (6) 1012-7.
Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000629
Last Updated on STN: 20021219
Entered Medline: 20000621

AB BACKGROUND & AIMS: Many reports indicate that nonsteroidal anti-inflammatory drugs (NSAIDs) have antineoplastic effects, but the precise molecular mechanism(s) responsible are unclear. We evaluated the effect of cyclooxygenase (COX) inhibitors (NSAIDs) on human colon carcinoma cells (HCA-7) and identified several genes that are regulated after treatment with NS-398, a selective COX-2 inhibitor. METHODS: Differential display **polymerase** chain reaction cloning techniques were used to identify genes regulated by treatment with NSAIDs and selective COX-2 inhibitors. RESULTS: A prostate apoptosis response 4 (Par-4) gene was up-regulated after NSAID treatment. Par-4 was first isolated from prostate carcinoma cells undergoing apoptosis, and expression of Par-4 sensitized **cancer** cells to apoptotic stimuli. Par-4 levels were increased in cells treated with COX inhibitors such as NS-398, nimesulide, SC-58125, and sulindac sulfide. Treatment of HCA-7 cells with these agents also induced apoptotic cell death. CONCLUSIONS: The results suggest that regulation of Par-4 contributes to the proapoptotic effects of high-dose COX inhibitors (NSAIDs) by serving as a downstream mediator leading to initiation of programmed cell death.

```
AB    . . . . cells (HCA-7) and identified several genes that are regulated
      after treatment with NS-398, a selective COX-2 inhibitor.  METHODS:
      Differential display polymerase chain reaction cloning
      techniques were used to identify genes regulated by treatment with NSAIDs
      and selective COX-2 inhibitors.  RESULTS: A.  .  .  was up-regulated after
      NSAID treatment.  Par-4 was first isolated from prostate carcinoma cells
      undergoing apoptosis, and expression of Par-4 sensitized cancer
      cells to apoptotic stimuli.  Par-4 levels were increased in cells treated
      with COX inhibitors such as NS-398, nimesulide, SC-58125, and.  .  .
CT    . . . . pharmacology
      *Apoptosis: DE, drug effects
       Apoptosis: GE, genetics
       Blotting, Northern
       Blotting, Western
       Carrier Proteins: AN, analysis
      *Carrier Proteins: GE, genetics
         Colonic Neoplasms
       Cyclooxygenase Inhibitors: PD, pharmacology
       DNA Fragmentation
       Gene Expression: DE, drug effects
       Gene Expression: PH, physiology
       Humans
         Intestinal Mucosa: CH, chemistry
        *Intestinal Mucosa: CY, cytology
         Intestinal Mucosa: EN, enzymology
      *Intracellular Signaling Peptides and Proteins
      *Nitrobenzenes: PD, pharmacology
       Protein Kinase C: ME, metabolism
       Pyrazoles: PD, pharmacology
.  .  . Support, U.S. Gov't, Non-P.H.S.
       Research Support, U.S. Gov't, P.H.S.
      *Sulfonamides: PD, pharmacology
       Sulindac: AA, analogs & derivatives
       Sulindac: PD, pharmacology
         Tumor Cells, Cultured
RN    123653-11-2 (N-(2-cyclohexyloxy-4-nitrophenyl)methanesulfonamide);
      162054-19-5 (1-((4-methylsulfonyl)phenyl)-3-trifluoromethyl-5-(4-
      fluorophenyl)pyrazole); 32004-67-4 (sulindac sulfide); 38194-50-2
      (Sulindac); 51803-78-2 (nimesulide)


=> d his

     (FILE 'HOME' ENTERED AT 09:22:46 ON 14 DEC 2005)

     FILE 'REGISTRY' ENTERED AT 09:22:55 ON 14 DEC 2005
                E "SULINDAC"/CN 25
L1            1 S E3

     FILE 'CAPLUS' ENTERED AT 09:23:34 ON 14 DEC 2005
L2         1426 S L1
L3       254068 S GASTROINTESTINGAL OR ESOPHAG? OR GASTIC? OR INTESTIN? OR COLO
L4      1099978 S CANCER? OR TUMOR? OR NEOPLAS? OR POLYP?
L5        65506 S L4 AND L3
L6          234 S L5 AND L2
L7       243958 S ORAL?
L8           30 S L7 AND L6
L9          186 S L2 (L) L4
L10         121 S L9 AND L3
L11          14 S L10 AND L7
L12           9 S L11 NOT PY>2002
L13     1945587 S LIPSOM? OR MICROSPHER? OR ENCAPSULAT? OR POLYMER?
L14           0 S L13 AND L12
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L15          443 S L4 AND L2
L16           12 S L9 AND L13
L17            3 S L16 NOT PY>2002

     FILE 'MEDLINE' ENTERED AT 09:35:28 ON 14 DEC 2005
L18          919 S SULINDAC/CN
L19      1879233 S CANCER? OR TUMOR? OR NEOPLAS? OR POLYP?
L20       428581 S GASTROINTESTINGAL OR ESOPHAG? OR GASTIC? OR INTESTIN? OR COLO
L21       125328 S L19 AND L20
L22          175 S L21 AND L18
L23       407843 S LIPOSOM? OR MICROSPHER? OR ENCAPSULAT? OR POLYMER?
L24            8 S L23 AND L22
L25            6 S L24 NOT PY>2002

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COST IN U.S. DOLLARS                                  SINCE FILE       TOTAL
                                                           ENTRY     SESSION
FULL ESTIMATED COST                                         3.52       73.53

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CA SUBSCRIBER PRICE                                         0.00       -3.65

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FILE LAST UPDATED: 13 Dec 2005  (20051213/ED)

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=> s liposom? or microspher? or encapsulat? or polymer?
         48683 LIPOSOM?
         27180 MICROSPHER?
         55572 ENCAPSULAT?
       1820552 POLYMER?
         84067 POLYMD
         84067 POLYMD
                 (POLYMD)
         31147 POLYMG
        326031 POLYMN
          8505 POLYMNS
        327118 POLYMN
                 (POLYMN OR POLYMNS)
       1885881 POLYMER?
                 (POLYMER? OR POLYMD OR POLYMG OR POLYMN)
L26    1984458 LIPOSOM? OR MICROSPHER? OR ENCAPSULAT? OR POLYMER?
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=> s l9 and l26
L27         15 L9 AND L26

=> s liposom? or microspher? or encapsulat?
         48683 LIPOSOM?
         27180 MICROSPHER?
         55572 ENCAPSULAT?
L28     122087 LIPOSOM? OR MICROSPHER? OR ENCAPSULAT?

=> s l28 and l9
L29         11 L28 AND L9

=> s l29 not py>2002
       3346380 PY>2002
L30          0 L29 NOT PY>2002

=> s l29 not py>2003
       2266400 PY>2003
L31          0 L29 NOT PY>2003

=> d l29 ibib 1-4

L29  ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:591975  CAPLUS
DOCUMENT NUMBER:          143:53482
TITLE:                    Method for inhibiting the growth of gastrointestinal
                          tract tumors
INVENTOR(S):              Egilmez, Nejat K.
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 21 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE       APPLICATION NO.         DATE
     ---------------     ----   --------   --------------------    --------
     US 2005147689        A1    20050707   US 2003-748003          20031230
     CA 2491338           AA    20050630   CA 2004-2491338         20041223
PRIORITY APPLN. INFO.:                     US 2003-748003      A   20031230

L29  ANSWER 2 OF 11  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:14227  CAPLUS
DOCUMENT NUMBER:          142:107439
TITLE:                    Cardiolipin synthesis inhibitor for treatment of
                          cardiovascular disorders, and obesity
INVENTOR(S):              Jamil, Haris; Ahmad, Moghis U.; Ahmad, Imran
PATENT ASSIGNEE(S):       Neopharm, Inc., USA
SOURCE:                   PCT Int. Appl., 48 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE       APPLICATION NO.         DATE
     ---------------     ----   --------   --------------------    --------
     WO 2005000318        A2    20050106   WO 2004-US20104         20040623
     WO 2005000318        A3    20050414
     WO 2005000318        B1    20050526
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
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            CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
            GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
            LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
            NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
            TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
        RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
            AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
            EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
            SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
            SN, TD, TG
PRIORITY APPLN. INFO.:                       US 2003-480669P     P  20030623

L29  ANSWER 3 OF 11  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:877933  CAPLUS
DOCUMENT NUMBER:          141:365149
TITLE:                    Anti-PSGL-1 antibodies and scFv fragments for
                          diagnosis, prognosis and therapy of cancer,
                          metastasis, autoimmune disease and inflammation
INVENTOR(S):              Levanon, Avigdor; Ben-Levy, Rachel; Plaksin, Daniel;
                          Szanton, Esther; Hagai, Yocheved; Mar-Chaim, Hagit
                          Hoch
PATENT ASSIGNEE(S):       Israel
SOURCE:                   U.S. Pat. Appl. Publ., 49 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND    DATE        APPLICATION NO.         DATE
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     US 2004208877        A1     20041021    US 2003-611588          20030630
PRIORITY APPLN. INFO.:                       US 2002-393491P     P  20020701

L29  ANSWER 4 OF 11  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2004:856929  CAPLUS
DOCUMENT NUMBER:          141:348831
TITLE:                    Antibodies specific to epitopes involving cell
                          rolling, metastasis and inflammation for treatment of
                          tumor, restenosis, thrombosis, autoimmune disease and
                          inflammation
INVENTOR(S):              Lazarovits, Janette; Nimrod, Abraham; Hoch, Mar-Chaim
                          Hagit; Levanon, Avigdor
PATENT ASSIGNEE(S):       Israel
SOURCE:                   U.S. Pat. Appl. Publ., 22 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND    DATE        APPLICATION NO.         DATE
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     US 2004202665        A1     20041014    US 2003-610843          20030630
PRIORITY APPLN. INFO.:                       US 2002-393453P     P  20020701


=> file pctfull
COST IN U.S. DOLLARS                               SINCE FILE       TOTAL
                                                        ENTRY     SESSION
FULL ESTIMATED COST                                     23.21       96.74

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)         SINCE FILE       TOTAL
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MOST RECENT UPDATE WEEK:       200549        <200549/EW>
FILE COVERS 1978 TO DATE

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http://www.stn-international.de/stndatabases/details/ipc_reform.html <

=> s SULINDAC
L32        2826 SULINDAC

=> s l32/ab
L33           9 (SULINDAC/AB)

=> s cancer? or tumor? or neoplas? or polyp?
          73935 CANCER?
          61948 TUMOR?
          21353 NEOPLAS?
         153344 POLYP?
L34      196562 CANCER? OR TUMOR? OR NEOPLAS? OR POLYP?

=> s l34 and l33
L35           7 L34 AND L33

=> s gastrointestingal or esophag? or gastic? or intestin? or colorect?
              4 GASTROINTESTINGAL
          11126 ESOPHAG?
             83 GASTIC?
          38774 INTESTIN?
           8423 COLORECT?
L36       47131 GASTROINTESTINGAL OR ESOPHAG? OR GASTIC? OR INTESTIN? OR COLOREC
                T?

=> s gastrointestinal or esophag? or gastic? or intestin? or colorect?
          28847 GASTROINTESTINAL
              9 GASTROINTESTINALS
          28851 GASTROINTESTINAL
                  (GASTROINTESTINAL OR GASTROINTESTINALS)
          11126 ESOPHAG?
             83 GASTIC?
          38774 INTESTIN?
           8423 COLORECT?
L37       59284 GASTROINTESTINAL OR ESOPHAG? OR GASTIC? OR INTESTIN? OR COLORECT
                ?

=> s l37 and l35
L38           7 L37 AND L35

=> s liposom? or microspher? or encapsulat?
          40590 LIPOSOM?
          15203 MICROSPHER?
          61501 ENCAPSULAT?
L39       90511 LIPOSOM? OR MICROSPHER? OR ENCAPSULAT?
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=> s l39 and l38
L40           2 L39 AND L38

=> d ibib 1-2

L40    ANSWER 1 OF 2       PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:          2001035956 PCTFULL  ED 20020820
TITLE (ENGLISH):           USE OF NSAIDs FOR THE TREATMENT OF PANCREATIC
                           CANCER
TITLE (FRENCH):            UTILISATION DES AINS DANS LE TRAITEMENT DU
                           CANCER DU PANCREAS
INVENTOR(S):               MARSHALL, Mark, Steven;
                           SWEENEY, Christopher, J.;
                           YIP-SCHNEIDER, Michelle, T.;
                           CROWELL, Pamela, L.
PATENT ASSIGNEE(S):        ADVANCED RESEARCH AND TECHNOLOGY INSTITUTE, INC.;
                           MARSHALL, Mark, Steven;
                           SWEENEY, Christopher, J.;
                           YIP-SCHNEIDER, Michelle, T.;
                           CROWELL, Pamela, L.
DOCUMENT TYPE:             Patent
PATENT INFORMATION:

                           NUMBER              KIND     DATE
                           --------------------------------
                           WO 2001035956        A1 20010525
DESIGNATED STATES
      W:                   AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU
                           CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN
                           IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK
                           MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM
                           TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD
                           SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY
                           DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF
                           CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.:         WO 2000-US31410       A  20001115
PRIORITY INFO.:            US 1999-60/165,543       19991115

L40    ANSWER 2 OF 2       PCTFULL   COPYRIGHT 2005 Univentio on STN
ACCESSION NUMBER:          1999049859 PCTFULL  ED 20020515
TITLE (ENGLISH):           DFMO AND SULINDAC COMBINATION IN CANCER
                           CHEMOPREVENTION
TITLE (FRENCH):            COMBINAISON DE DFMO ET DE SULINDAC DANS LA
                           CHIMIOPREVENTION DU CANCER
INVENTOR(S):               GERNER, Eugene, W.;
                           MEYSKENS, Frank, L., Jr.
PATENT ASSIGNEE(S):        THE ARIZONA BOARD OF REGENTS on behalf of THE
                           UNIVERSITY OF ARIZONA;
                           THE REGENTS OF THE UNIVERSITY OF CALIFORNIA;
                           GERNER, Eugene, W.;
                           MEYSKENS, Frank, L., Jr.
LANGUAGE OF PUBL.:         English
DOCUMENT TYPE:             Patent
PATENT INFORMATION:

                           NUMBER              KIND     DATE
                           --------------------------------
                           WO 9949859           A1 19991007
DESIGNATED STATES
      W:                   AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK
                           EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP
                           KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL
                           PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN
                           YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ
                           MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU
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MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD
TG

APPLICATION INFO.: WO 1999-US6693 A 19990326
PRIORITY INFO.: US 1998-60/079,850 19980328

=> d kwic 1

L40 ANSWER 1 OF 2 PCTFULL

TIEN USE OF NSAIDs FOR THE TREATMENT OF PANCREATIC **CANCER**

TIFR UTILISATION DES AINS DANS LE TRAITEMENT DU **CANCER** DU PANCREAS

ABEN The invention provides a method comprising the use of non-steroidal antiinflammatory drugs (NSAIDs), particularly **sulindac** or its analogs to treat pancreatic **cancer**.

DETD USE OF NSAIDs FOR THE TREATMENT OF PANCREATIC **CANCER**
Backgrround of the Invention
Cancer of the pancreas ranks 'ust behind lung **cancer**
, colon **cancer**, and
breast **cancer** as the most common cause of death by
cancer (1). It is more
common among men, and men between the ages of 60 and 70 are most at
risk.

/

The cause of pancreatic **cancer** is unknown.

. . .
which are not fully understood, usually is
significant. The average loss is about 25 pounds. Jaundice occurs if
the **cancer**
blocks the common bile duct. The survival rate with pancreatic
cancer is poor.

By the time the malignant **tumor** is identified, it often has
spread (metastasized)
to other parts of the body. The median survival is little more than six.
. .

Often the **tumor** cannot be removed by surgery, either because
it has
invaded vital structures that cannot be removed or because it has spread
to
distant sites. Chemotherapy and radiation therapy can be used on the
tumor,
although these treatments often are not beneficial.

. . .
Easton, PA (18th ed., 1990) at pages
1115
There is a large amount of literature on the effect of NSAIDs on
cancer,
particularly colon **cancer**. For example, see H. A. Weiss et
al., Scand J.

. . .
in vitro, but that
indomethacin, ketoralac and NS-398, did not. Sulindac has been
investigated in
combination therapy for the treatment of colon **cancer**. See, H.
M. Verheul et al.,
Brit- J. Cance , 79, 114 (1999); F. A. Sinicrope et al., Clin.
Cancer Res-, 2, 37
(1996); and M. Mooghen et al., J. Pathol., LI]6, 394 (1988).

C. P. Duffy et al., Eur. J. **Cancer**, 34, 1250 (1998), reported
that the

cytotoxicity of certain chemotherapeutic drugs was enhanced when they were combined with certain non-steroidal anti-inflammatory agents. The effects observed against human lung **cancer** cells and human leukemia cells were highly specific and not predictable; i.e., some combinations of NSAID and agent were effective and some. . .

. . . .
a PCT application (WO98/18490) on October 24, 1997, directed to a combination of a substrate for MRP, which can be an anti- **cancer** drug, and a NSAID that increases the potency of the anti-**cancer** drug.

Therefore, a continuing need exists for methods to control **cancers**, and to increase the potency of anti-**cancer** drugs with relatively non-toxic agents.

Summ= of the Invention
In one aspect, the present invention provides a therapeutic method to treat pancreatic **cancer**, comprising administering to a mammal afflicted with pancreatic **cancer** an amount of a NSAID, preferably sulindac ((Z) fluoro methyl-1-[[4-(methylsulfinyl)phenyl] methylene]-IH-Indene acetic acid), or an analocr thereof, preferably one that is a COX-2 inhibitor, effective to inhibit the viability of pancreatic **cancer** cells of said mammal. The present invention also provides a method of increasing the susceptibility of human pancreatic **cancer** cells to a chemotherapeutic agent comprising contacting the cells with an effective sensitizing amount of a NSAID, preferably sulindac, or said analog thereof Thus, the invention provides a therapeutic method for the treatment of a human or other mammal afflicted with pancreatic **cancer**, wherein an effective amount of an NSAID, preferably sulindac or said analog thereof is administered to a subject afflicted with pancreatic **cancer** and undergoing treatment with a chemotherapeutic (antineoplastic) agent.

Preferably, sulindac is administered in conjunction with one or more chemotherapeutic agents effective against pancreatic **cancer** such as gemcitabine or 5-FU.

A method of evaluating the ability of sulindac to sensitize pancreatic **cancer** cells to a chemotherapeutic agent is also provided. The assay method comprises: (a) isolating a first portion of pancreatic **cancer** cells ftom a human **cancer** patient; (b) measuring their viability; (c) administering sulindac, or said analog thereof, to said patient; (d) isolating a second portion of

pancreatic **cancer**
cells from said patient; (e) measuring the viability of the second portion of
pancreatic **cancer** cells; and (f) comparing the viability measured in step (e) with
the viability measured in step (b); wherein reduced viability in. . . .
(b) and (e) are carried out in the presence of the chemotherapeutic agent, as will be the case when the pancreatic **cancer** cells are
derived from the blood of a mammal afflicted with pancreatic **cancer**.

Thus, a **cancer** patient about to undergo, or undergoing, treatment for
pancreatic **cancer** can be rapidly evaluated to see if he/she will benefit from
concurrent chemotherapy and administration of sulindac or an analog thereof.
.
Description of the FiVures
Figure 1. Photocopy of a representative immunoblot of pancreatic adenocarcinomas and matched normal tissue. Lysates were prepared from **tumor**
(T) specimens obtained from six patients, three with matched normal (N) tissue
(sample numbers correspond to those listed in Table 1). Lysates. . . expresses neither COX- I or COX
Figure 2. Percent COX-2 expression in patient samples. Values of % COX-2 expression for all **tumor** samples, shown by solid circles, and non-nal
tissue, shown by open circles, from Table I are plotted. Values for mean, median
and range are indicated. The % COX-2 expression for the matched pancreatic
tumor/normal tissue sets is shown in the inset (n = I 1). Lines are drawn between
the corresponding **tumor** values, shown by solid circles, and non-nal values,
shown by the open circles. The difference in COX-2 expression between **tumor**
and non-nal specimens was determined to be statistically significant (P = 0.004).

Figure 3. COX-2 expression in pancreatic **tumor** cell lines. A) COX-2
expression in human pancreatic cell lines detected by immunoblot analysis. The
K-ras mutation status of each of the. . .

Figure 4. Effect of COX inhibitors on the growth of pancreatic **tumor**
cell lines. The cell lines BxPC-3, shown by the black bars, and PaCa-2, shown
by the hatched bars, were plated in the. . .

Figure 5. Prostaglandin E2 production. A) PGE2 levels in pancreatic **tumor** cell lines. Following incubation of exponentially growing cells with
15 gM arachidonic acid in serum-free media for one hour, PGE2 levels. . .

Figure 6 is a graph depicting the effect of a combination of sulindac

and
gemcitabine on the growth of pancreatic **tumor** cell line BxPC.

Figure 7 is a graph depicting the effect of a combination of sulindac and gemcitabine on the growth of pancreatic **tumor** cell line PaCa

Detailed Description of the Invention

Difficulty in achieving early diagnosis as well as the aggressive nature of pancreatic **cancer** contribute to the low survival rate of patients with pancreatic **cancer**. Since few options exist for the treatment of pancreatic **cancer,** it is important to identify potential targets for drug therapy. In an effort to gain more insight into pancreatic tumonigenesis] pancreatic **tumors** have been analyzed at the molecular level to detect genetic lesions. Activating mutations within the K-ras gene have been detected in up to 90% of pancreatic carcinomas, suggesting that activation of the Ras pathway is important in the development of pancreatic **cancer** (2). Experimental chemotherapeutic strategies for pancreatic **cancer** patients currently include drugs which target the Ras signal transduction pathway.

. . . .

For example, epidemiological studies have shown that prolonged use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce the risk of colon **cancer** by 40-50% (3). NSAIDs also inhibit chemically induced colon carcinomas in animal model systems (4). Since NSAIDs are known to inhibit cyclooxygenase. . . esters, and growth factors (5, 6). COX-2 expression has recently been shown to be elevated in several different types of human **cancer,** suggesting that the presence of COX-2 correlates with **cancer** development (7-1 1). Additional studies which directly link COX-2 to carcinogenesis include observations that human colon **cancer** cells expressing COX-2 acquire increased invasiveriess (12) and that COX-2 expressed in **intestinal** epithelial cells inhibits apoptosis (13). COX-2 expression in colon **cancer** cells has also been found to promote angiogenesis of co-cultured endothelial cells by stimulating the production of angiogenic factors (14). Furthermore, direct genetic evidence linking COX-2 to **colorectal tumorigenesis** was provided by a mouse model for human familial adenomatous **polyposis** (FA-P), an inherited condition leading to **colorectal cancer;** in this system, COX-2 gene knockouts and a specific COX-2 inhibitor were found to reduce the number of **intestinal polyps** formed (1 5).

The presence of oncogenic Ras has been associated with the induction of COX-2 expression in H-ras-transformed rat **intestinal** and mammary epithelial cellsaswellasinnon-smallcelllungcancercelllines(16-18). Toour knowledge, the association between oncogenic Ras and COX-2 expression has not ben explored in vivo. The high frequency of activating mutations within the K-ras gene in pancreatic **tumors** should enable us to investigate the relationship between oncogenic K-ras and COX-2 expression in vivo. In the present study, we evaluated COX-2 protein levels in primary human pancreatic adenocarcinomas. We further examined whether COX-2 expression correlated with K-ras mutation status in pancreatic **tumors** as well as in pancreatic **cancer** cell lines. In light of our data demonstrating elevated levels of COX-2 protein in primary pancreatic **tumors** and cell lines, we tested the effect of the COX inhibitors sulindac, indomethacin and NS-398 on cell growth and prostaglandin E2 production in human pancreatic **tumor** cell lines.

Cyclooxygenase-2 (COX-2) expression is upregulated in several types of human **cancers** and has also been directly linked to carcinogenesis. To investigate the role of COX-2 in pancreatic **cancer,** we evaluated COX-2 protein expression in primary human pancreatic adenocarcinomas (n = 23) and matched normal adjacent tissue (n = I 1) by immunoblot analysis. COX-2 expression was found to be significantly elevated in the pancreatic **tumor** specimens compared to normal pancreatic tissue. To examine whether the elevated levels of COX-2 protein observed in pancreatic **tumors** correlated with the presence of oncogenic K-ras, we determined the K-ras mutation status in a subset of the **tumors** and corresponding non-nal tissues. The presence of oncogenic K-ras did not correlate with the level of COX-2 protein expressed in the pancreatic adenocarcinornas analyzed. These observations were also confirmed in a panel of human pancreatic **tumor** cell lines. Furthermore, in the pancreatic **tumor** cell line expressing the highest level of COX-2 (BxPC-3), COX-2 expression was demonstrated to be independent of Erkl/2 Map kinase activation. The. . . lack of correlation between COX-2 and oncogenic K-ras expression suggests that Ras activation may not be sufficient to inducing COX-2 expression in pancreatic **tumor** cells and that the aberrant activation of signaling pathways other than Ras may be required for up-regulating COX-2 expression. We also. . . report that the COX inhibitors sulindac, indomethacin, and NS-398 inhibited cell growth in both COX positive (BxPC-3) and COX negative (PaCa-2) pancreatic

tumor
cell lines. However, suppression of cell growth by indomethacin and
NS-398
was sigm icantly greater in the BxPC-3 cell line compared to. . .
that COX-2 may play an important role in pancreatic
tumongenesis and therefore be a promising chemotherapeutic target for
the
treatment of pancreatic **cancer**.

I 0
Other NSAIDs, including indomethacin and NS-398 also the
growth of pancreatic **tumor** cell lines, as discussed
hereinbelow, and can also be
used in the present method, alone, or preferably in combination with
sulindac.

. . .
or infusion in dosages of about 500-4000 Mg/M2 /week
for up to 7 weeks/cycle for treatment of localized or metastatic
pancreatic **cancer**
(adenocarcinoma of the pancreas). It can also be administered in
conjunction
with other anti-**cancer** agents, such as 5-FU. See, PDR (53rd
ed., 1999) at pages
1578
The effect of sulindac or NS-398 alone and in combination with
gemcitabine on the growth of pancreatic **tumor** cells BxPC-3 and
PaCa-2 was
investigated. Treatment with the drug combinations inhibited the growth
of both
cell lines to a greater extent. . . NF-KB DNA
binding activity was inhibited by parthenolide treatment. These results
suggest
that anti-inflammatory drugs may enhance the effectiveness of
gemcitabine
against pancreatic **tumors**.

. . .
of a prophylactic or therapeutic dose of sulindac, an
analog thereof or a combination thereof, in the acute or chronic
management of
cancer, i.e., pancreatic caner, will vary with the stage of
the **cancer**, such as the
solid **tumor** to be treated, the chemotherapeutic agent(s) or
other anti-**cancer**
therapy used, and the route of administration. The dose, and perhaps the
dose
frequency, will also vary according to the age, body. . .

. . .
5 chemotherapy regimen. The sulindac, in some cases, may be combined
with the
same carrier or vehicle used to deliver the anti-**cancer**
chemotherapeutic agent.

. . .
sterile powders comprising the
active ingredient which are adapted for the extemporaneous preparation
of sterile
injectable or infusible solutions or dispersions, optionally
encapsulated in
liposomes. In all cases, the ultimate dosage form must be
sterile, fluid and stable
under the conditions of manufacture and storage. The. . . like),
vegetable oils, non-toxic glyceryl esters, and suitable
mixtures thereof The proper fluidity can be maintained, for example, by
the

formation of **liposomes**, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention. . .

. . . were obtained from the Indiana University Tissue Procurement Laboratory and the Cooperative Human Tissue Network (CHTN) which is funded by the National **Cancer** Institute. A total of 23 primary human pancreatic **cancer** specimens were analvzed in this study.

. . . within I hour of surgical removal and subsequently stored at -80'C. Paraffin sections were prepared from a subset of the specimens. All **tumor** specimens used in this study were examined by a pathologist and classified as primary pancreatic adenocarcinornas.

5. Statistical Analysis. The presence of statistically significant elevation of COX-2 protein between **cancer** specimens and corresponding normal adjacent tissues was determined by the nonparametric signed rank test. A two-way analysis of variance (ANOVA) was used. . .

6. Cell Lines. The human pancreatic **tumor** cell lines (AsPC-1, BxPC-3, Capan-1, Capan-2, HPA-F-11, Hs766T, PaCa-2 and PANC-1) were obtained from the American Type Culture Collection (ATCC, Rockville, MD). . .

. . . Undetectable levels of COX-2 protein were observed in each of the normal specimens. In contrast, COX-2 protein expression in the pancreatic 5 **tumor** tissues ranged from undetectable (sample #2 1) to slight/moderate (samples #12, 14, 20) to high levels (samples #9, 22). COX-1 protein was observed in both pancreatic **tumor** and normal tissues, although the level of expression was variable and not consistently elevated in the **tumor** specimens (Figure 1). Similar levels of p21' and actin expression were found in both the **tumor** and corresponding normal tissues (Figure 1).

. . . narrower range (0 3%) of COX-2 expression in the normal tissues. Both the mean and median COX-2 expression were higher in the **tumor** samples, suggesting that COX-2 expression is elevated in pancreatic adenocarcinomas compared to normal tissue. The difference in COX-2 expression between the pancreatic **tumor** and corresponding normal tissue was determined to be statistically significant ($P = 0.004$) (Figure 2, inset).

. . . less than 5% respectively, which corresponds closely with visual detection in the immunoblots. According to these criteria, 6 out of 11 (55%) **tumor** samples in the matched

tissue sets were
COX-2 positive. Similarly, 13 out of the 23 (56%) total **tumor**
specimens
analyzed were COX-2 positive; in contrast, all the normal tissue samples
(n
I 1) were COX-2 negative.

h-nmunohistochemical staining of the pancreatic **tumor**
specimens
demonstrated that COX-2 expression was localized to the carcinoma cells
and
was not detectable in the stromal compartment of the **tumors**
(Figure 3).

Example 2
COX-2 expression and K-ras mutation in pancreatic **tumors** and
cell lines
To determine if COX-2 expression levels correlated with the K-ras
mutation status of the **tumors**, genomic DNA was isolated from a
subset of the
tissue specimens and screened for the presence of K-ras mutations at
codon. . .
. . .
the
normal tissues analyzed were wild-type at codon 12 (GGT = Gly) and codon
13
(GGC = Gly). Of the 13 pancreatic **cancer** specimens analyzed,
one specimen
had a mutation at codon 13 whereas IO samples were mutated at codon 12,
corresponding to a K-ras. . . extent of COX-2 protein
expression. For example, some samples expressed high levels of COX-2
protein
and possessed a mutation in K-ras (i.e., **tumor** samples #9, 16
and 22); however,
other samples which had mutated K-ras expressed little or no COX-2
protein
(i.e., **tumor** samples #3, 17, 18, 19, and 21).
. . .
with known K-ras mutation status (25, 26). Both the frequency and
variability in the quantity of COX-2 expressed in the pancreatic
tumor cell lines
reflected our findings in the primary pancreatic adenocarcinomas. Of the
eight
human pancreatic **tumor** cell lines analyzed, only three of the
seven cell lines
expressing oncogenic K-ras exhibited detectable levels of COX-2 protein
(Capan-1, Capan-2 and. . . (Figure 4B). Taken
together, our results suggest that activation of the Ras pathway is not
sufficient
for mediating COX-2 uprecrulation in pancreatic **tumor** cells.
We also compared
the level of COX-2 expression in three hamster pancreatic cell lines,
The
D27/K-ras and B 12/13 transformed cell. . . parental line (Figure 4Q.
These results confirm our conclusion that
Ras activation alone is not sufficient for upregulating COX-2 expression
in
pancreatic **cancer** cells and suggest that additional events
which occur following
exposure to chemical carcinogens may be required.

To examine whether COX-2 expression could be induced in the human
pancreatic **cancer** cell lines, four cell lines were

serum-starved and subsequently
treated with IO% FCS for various time periods (F1 crure 4D). In. . .
. . .
is activated (unpublished observations), again demonstrating
that Erk 1/2 activation is not sufficient for inducing COX-2 expression
in the
COX negative pancreatic **tumor** cells. We observed similar
results upon
treating the cell lines with the **tumor** promoter, PMA
(unpublished observations).

Example 3
Treatment of pancreatic **tumor** cell lines with cyclooxygenase
inhibitors
The COX positive human pancreatic **tumor** cell lines, BxPC-3,
and the
COX negative cell line, PaCa-2, were treated with the COX inhibitors
sulindac, indomethacin, or NS Sulindac and. . . was measured after
three days of treatment (Figure 5). All three
inhibitors were found to suppress cell growth in both pancreatic
tumor cell lines
in a dose-dependent manner. However, indomethacin and NS-398 were found
to
inhibit cell growth to a greater extent in the. . .

To evaluate the functional activity of COX-2 in the human pancreatic
tumor cell lines, prostaglandin E2 (PGE,) production was
measured by
enzymeimmunoassay (Figure 6A). PGE2 production was elevated in the BxPC-
3, Capan-1, Capan-2. . .

These data demonstrate that the combination of sulindac and gemcitabine
is more effective than either compound alone in pancreatic **tumor**
cells.
. . .
as well as inflammatory agents (5, 6,
29). Recent studies have shown that COX-2 expression is upregulated in a
variety of human **cancers**, including colon, lung, gastric,
pancreatic and
esophageal (7-1 1). In the present study, we report that
elevated levels of COX-2
protein are expressed in human pancreatic **tumors** compared to
barely detectable
levels in the matched non-nal pancreatic tissue, suggesting that
increased
expression of COX-2 protein correlates with pancreatic tunionigenesis.
Our
results confirm a recent report demonstrating upregulation of COX-2 RNA
and
protein in pancreatic **tumors** and localization of COX-2 in
malignant epithelial
cells (I 1). An earlier study demonstrated that the expression of group
11
phospholipase A2,. . . phospholipids, was higher in pancreatic ductal
adenocarcinomas
compared to normal pancreatic tissue (30). In addition, the development
of N-
nitrosobis(2-oxopropyl)amine (BOP)-initiated pancreatic **tumors**
in hamsters was
inhibited bv the administration of two prostaglandin synthesis
inhibitors,
phenylbutazone and indomethacin (3 1). Together with our observations
in. . . that increased prostaglandin production due to

the increased expression of COX-2 may be an important event in the multi-step progression towards pancreatic **tumor** formation.

. . .

as well as prostaglandin E2 were detected in Ras-transformed mammary epithelial cells (C57/MG) cells (I 7). In human non-small cell lung **cancer** (NSCLQ cell lines expressing oncogenic K-Ras, increased PGE2 production was mediated by constitutively high expression of cytosolic, phospholipase A, and COX-2 compared. . . . the expression of detectable levels of COX-2 protein. A possible explanation for the lack of COX-2 expression in a subset of the **tumors** with oncogenic Ras is that Erkl/2 activity may be down-regulated in pancreatic carcinomas (26). Moreover, even in the two pancreatic **tumor** samples which did show elevated levels of activated Erkl/2 (samples #4 and 21, data not shown), only low levels of COX-2. . . . in the present study, suggesting that Erkl/2 activation alone is not sufficient for inducing COX-2 expression. These findings suggest that within the **tumor** environment, the presence of oncogenic K-ras does not directly result in increased COX-2 expression in pancreatic **cancer**.

Similar conclusions were also reached upon analysis of pancreatic **cancer** cell lines, which were examined since they represent a homogenous population of cells as opposed to primary **tumor** tissue which is heterogenous. Despite activating K-ras mutations in seven out of the eight lines, only three of the lines with mutated. . . . of COX-2 expression. Activation of other signaling pathways in addition to Ras may cooperate to determine the extent of COX-2 expression in **cancer** cells. Such pathways may include the p38 mitogen-activated protein kinase which has been reported to regulate the induction of COX-2 in lipopolysaccharide-treated. . . . the cell type as well as the stimulus. Further experiments will be required to delineate which signaling pathways are function in pancreatic **tumor** cells.

. . .

expressing cell lines. These data suggest that the COX inhibitors exert their inhibitory effects by both COX/PGE,-dependent and -independent pathways in pancreatic **tumor** cell lines.

The detection of elevated levels of COX-2 in a variety of human **cancers** combined with the chemopreventative effect of NSAIDs in colon **cancer** demonstrate that COX-2 is an important participant in carcinogenesis. The

reported biological consequences of COX-2 upregulation include inhibition of apoptosis (13), increased metastatic potential (12) and promotion of anglogenesis (14). These events may contribute to cell transformation and **tumor** progression.

COX-2 expression was noticeably elevated in 55% of the patient pancreatic **tumor** samples analyzed, identifying COX-2 as a new target for chemotherapy.

These results demonstratincy the ability of COX inhibitors to inhibit pancreatic **tumor** cell growth and PGE, production in vitro indicate that NSAIDs may be effective in the treatment of pancreatic **cancer** patients, for whom few treatment options currently exist. COX-2 expression is also useful as a prognostic or diagnostic tool.

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TABLE 1. Analysis of Patient Samples
Tissue Sample' Tissue Type % COX-2 b % **Cancer**' K-raE
I pancreatic adenocarcinorna 7.0 10 WT
2 pancreatic adenocarcinorna 2.0 95
3 pancreatic adenocarcinoma 0.2 15 GGC to CG,
4 pancreatic adenocarcinorna 3.6. . . N nornial 0.1 -
12 pancreatic adenocarcinorna I 15
14 pancreatic adenocarcinorria 31 ND
Tissue Sample a Tissue Type % COX-2 b % **Cancer**' K-ras
1 5 pancreatic adenocarcinonia 7.8 25 GGT to
15N normal 4.3 - I
1 6 pancreatic adenocarcinoma 66 35 GGT to
16N non-nal. . .

c The percent **cancer** was determined by visualization following hematoxylin/eosin staining of slides prepared from paraffin sections.

CLMEN I . A method of reducing the viability of pancreatic **cancer** cells comprising contacting the **cancer** cells with an effective amount of an

NSAID.

2 A method of increasing the susceptibility of mammalian pancreatic **cancer** cells to a chemotherapeutic agent comprising contacting the cells with an effective sensitizing amount of an NSAID.

4 The method of claim I or 2 wherein the mammalian **cancer** cells are human **cancer** cells.

5 The method of claim 3 wherein the sulindac or the analog thereof is administered to a human **cancer** patient.

6 The method of claim 5 wherein the **cancer** patient is undergoing treatment with a chemotherapeutic a2ent.

. . .

9 A method of evaluating the ability of sulindac or an analog thereof that is a COX-2 inhibitor to sensitize pancreatic **cancer** cells to a chemotherapeutic agent comprising:
(a) isolating a first portion of pancreatic **cancer** cells from a human pancreatic **cancer** patient;
(b) measuring their viability;
(c) administering sulindac or the analog thereof to said patient;
(d) isolating a second portion of pancreatic **cancer** cells from said patient;
(e) measuring the viability of the second portion of pancreatic **cancer** cells; and
(f) comparing the viability measured in step (e) with the viability measured in step (b); wherein reduced viability in step (e) indicates. . .

. . .

T N T
COX-2 mm 40- cwIIw
C OX- 1
p2i ras
Actin
]1]] VW Iwo ow
C/ (]-)
/8
loo -
90 - lo(
9CF
80-
9
7CF
70-
60-
40
3Y
to 50-
a
cw
C*4 26
40- 1 Cy
0
TUMOR NORMAL

30 -
20-
lo-
8
0- 00
TUMOR NORMAL
(n--23)
ylwMian = 5.2% median = 02%
nwan = 15.2 +/- 24.9% mcan 0.83 +/- 1.3%
v2mge ≐ 0 - 93% map 0. . . Sulindac IndometIL NS-398
% inhibition: 0 07 90 F957 98 759 86
/8
Effect of Sulindac + Gemcitabine on the growth of the pancreatic **tumor** cell line, BxPC-3 (day 3)
125 -
100 I Gem alone
75 -
1,100+ e
50 - T
em
sul, 500 + Gem
0 5 10 15 20. . . and Technology Institute, Inc.
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Sweeney, Christopher J.
Yip-Schneider, Michele T.
Crowell, Pamela L.
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<150> US 60/165,543
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<160> 2
<170> FastSEQ for Windows Version 4.0
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<213> Homo sapiens
<400> 1
atgactgaat ataaacttgt 20
<210> 2
<211>. . . search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ,, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS, **CANCERLIT**
C. DOCUMENTS CONSIDERED TO BE RELEVANT
Category Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.
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